EUROPEAN CHEMICALS AGENCY

Helsinki, 25 September 2019

Addressee: [redacted]

Decision number: CCH-D-2114482462-47-01/F
Substance name: Zirconium praseodymium yellow zircon
EC number: 269-075-7
CAS number: 68187-15-5
Registration number: [redacted]
Submission number subject to follow-up evaluation: [redacted]
Submission date subject to follow-up evaluation: 1 December 2017

DECISION TAKEN UNDER ARTICLE 42(1) OF THE REACH REGULATION

By decision CCH-D-2114289282-44-01/F of 12 December 2014 ("the original decision") ECHA requested you to submit information by 19 December 2017 in an update of your registration dossier.

Based on Article 42(1) of Regulation (EC) No 1907/2006 (the 'REACH Regulation'), ECHA examined the information you submitted with the registration update specified in the header above, and concludes that

Your registration still does not comply with the following information requirement:

Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

The respective Member State competent authority (MSCA) and National enforcement authority (NEA) will be informed of this decision. They may consider enforcement actions to secure the implementation of the original decision and exercise the powers reserved to them under Article 126 of Regulation No 1907/2006 (penalties for non-compliance) for the period during which the registration dossier was not compliant[1].

[1] See paragraphs 61 and 114 of the judgment of 8 May of the General Court of the European Court of Justice in Case T-283/15 Esso Raffinage v. ECHA

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, shall be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under http://echa.europa.eu/regulations/appeals.

Authorised[2] by Wim De Coen, Head of Unit, Hazard Assessment

[2] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

Appendix 1: Reasons

Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

In decision CCH-D-2114289282-44-01/F ("the original decision") you were requested to submit information derived with the registered substance for Pre-natal developmental toxicity endpoint.

In the updated registration subject to follow-up evaluation, you have provided an adaptation according to Annex IX, Section 8.7, Column 2, and according to Annex XI, Section 1.2.

Regarding the Annex IX, Section 8.7, Column 2 adaptation *"The studies do not need to be conducted if the substance is of low toxicological activity (no evidence of toxicity seen in any of the tests available), it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure (e.g. plasma/blood concentrations below detection limit using a sensitive method and absence of the substance and of metabolites of the substance in urine, bile or exhaled air) and there is no or no significant human exposure."* As further explained below, ECHA considers that none of the criteria are met.

With regards to *"low toxicological activity"*, ECHA notes that in the newly generated 28-day limit dose test the following findings were observed at 1000 mg/kg bw/day. You reported statistically significant differences in haematological parameters, namely increased platelet counts in females and increased absolute monocyte and basophilic granulocyte counts in males, statistically significantly decreased albumin levels in females and increased glucose and decreased chloride levels in males. In male rats, you reported statistically significant increase in hindlimb grip strength. Furthermore you reported statistically significant organ weight changes in males (increased absolute left epididymis weight, increased absolute right testis weight, increased absolute left kidney weight, increased absolute right kidney weight, increased relative spleen weight, increased absolute spleen weight) and females (decreased relative heart weight). You considered the findings not test item related, however ECHA is of the opinion that this does not support a conclusion of *"no evidence of toxicity seen in any of the tests available"*.

With regards to *"absence of systemic absorption via relevant routes of exposure"*, ECHA notes that in the non-guideline single dose mass balance study with the registered substance, you reported recoveries of 102% Praseodymium and 74.3% of Zirconium. Further, you reported measurable quantities of Praseodymium excreted in urine during the first day in the single dose mass balance study (no data given for Zirconium). Based on the information provided, ECHA is of the opinion that it cannot be concluded that there is *"no systemic absorption via relevant routes of exposure"*.

With regards to *"no or no significant human exposure"*, ECHA notes that you newly reported the following particle size distribution data of the registered substance: D10: 3.3 µm; D50: 9.6 µm; D90: 21.8 µm. Therefore, ECHA observes that the registered substance is inhalable (particles that enter the respiratory system via the nose or mouth, D <100 µm), and also respirable (the respirable fraction is the portion of inhalable particles that enter the deepest part of the lung, the non-ciliated alveoli (D <10 µm) with a 50% cut at 4 µm). ECHA notes also that although based on the concurrent particle size analysis via inhalation deposition modelling with MPPD (Multiple Path Particle Dosimetry) an important fraction of the

deposition occurs in the extra thoracic region, it is also predicted by the model that a fraction of the airborne material is deposited in the pulmonary alveoli (0.9%) and tracheo-bronchial region (0.8%). Additionally, ECHA observes that in the report on the occupational exposure assessment attached to IUCLID Section 13 [redacted] you describe spraying applications of the registered substance by downstream users. ECHA notes that spraying application are normally connected to a certain degree of exposure and while in table 18 of the document you describe the industrial spraying in enclosed settings, the professional spraying applications involve a worker directly working over the article which indicates inhalation exposure to the registered substance. ECHA is of the opinion that it cannot be concluded that there is *"no or no significant human exposure"*.

With respect to the adaptation according to the Annex XI, Section 1.2, ECHA observes that the sources of information do not allow concluding whether or not the registered substance has a particular dangerous property (i.e. developmental toxicity). In particular, none of the sources of information provides evidence about the potential of the registered substance to cause pre-natal developmental toxic effects, as the only repeated dose toxicity study available does not examine pre-natal developmental endpoints. Also, as already pointed above, in ECHA's view it cannot be concluded that the registered substance would show such general absence of toxicological activity and absorption, which would allow to conclude an absence of developmental toxicity as well.

In summary, ECHA observes that the information provided does not fulfil the adaptation requirements of the Annex IX, 8.7. Column 2 or Annex XI, Section 1.2.

As already stated in the original decision, according to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

In your comments to the draft decision you provided comments for each of the conditions of the above mentioned adaptation according to Annex IX, Section 8.7, Column 2.

As regards *"low toxicological activity"*, you provided new information from the newly generated 28-day limit dose test in order to demonstrate that the values of the main findings are within the historical control ranges. That information, which is not provided in the IUCLID dossier, based on your comments would allow to consider those individual observations as non-adverse. ECHA notes indeed that this information seems to indicate *"low toxicological activity"*. However, as stated below, other conditions of the adaptation according to column 2 of Annex IX section 8.7 are not met.

ECHA further notes that further to comparisons with historical control values, comparisons with internal controls of the 28-day limit test are relevant. ECHA considers that, the presence of multiple changes, compared with the internal controls, in haematological and clinical biochemistry parameters, as well as in organ weights and grip strength, seems to indicate that the substance is absorbed and enters into the systemic circulation to a certain extent to influence those parameters. This is relevant for the determining if systematic absorption via relevant routes of exposure takes place, as discussed below.

As regards *"absence of systemic absorption via relevant routes of exposure"* you refer to the mass balance study and urinary concentration data and also clarify that Zirconium excretion via urine was also negligible and below 0.000015% and that the control group showed a mean value of about 1.46 µg Zr/L whereas the dose group showed only slightly higher mean values of ca. 2.38 µg Zr/L. You acknowledge the lack of these data in the IUCLID file due to analytical problems at the time of submission. ECHA notes that as already stated above, in the non-guideline single dose mass balance study with the registered substance, you reported recoveries of 102% praseodymium and 74.3% of zirconium via urine and faeces and measurable quantities of praseodymium in urine (0.03 µg Pr/L). According to your new data there was also measurable quantities of zirconium in urine and higher, although only slightly, than among controls. ECHA considers that it cannot be concluded that there is *"absence of systemic absorption via relevant routes of exposure"*.

As regards *"no or no significant human exposure"* you claim that while the total deposition in the human respiratory tract predicted with the MPPD model is approximately 50%, only a very small sub-fraction (0.9%) of the inhalable particles will deposit in the pulmonary region of the respiratory tract, whereas the remaining portion is predicted to deposit in the tracheobronchial and extrathoracic region. Thus, the overwhelming majority of inhaled particles would be rapidly cleared to the gastrointestinal tract either by swallowing (particles depositing extrathoracically) or by mucociliary escalation and subsequent swallowing (particles deposited tracheobronchially). Based on this you conclude that oral route represents the major route of human exposure. ECHA understands this as an agreement to use the oral route to maximise systemic exposure in a pre-natal developmental toxicity study, where local effects in the respiratory tract are not investigated. Furthermore you clarify that the professional spraying application is a short-time and infrequent activity and relates to research and development work. You also provide a worst-case calculation assuming this task to be conducted for 15 minutes per shift (although reasonably assumed to only be conducted at maximum once a month) in order to illustrate the overall exposure contribution of this task. You also state that the percentage of the pigment in the spray is maximum [redacted]. ECHA notes that while this spray application is of short duration it nevertheless creates an opportunity for the worker to experience a high exposure to the aerosols that are created during that spraying task. Furthermore a concentration of [redacted] of pigment in the spraying application cannot be considered such a low concentration that there would be no significant exposure during the performance of that task. ECHA considers that it cannot be concluded that there is *"no or no significant human exposure"*.

Finally ECHA notes that in your comments to the draft decision your proposed also an adaptation based on a read across approach according to Annex XI section 1.5 of REACH Regulation. The provided read-across hypothesis is based on the bioavailability and toxicity of the three main compounds of the registered substance, praseodymium, zirconium oxide/hydroxide, and silica/silicates. However, you have only listed several studies which *'will be assessed further'*. Annex XI, Section 1.5 of the REACH Regulation states that "adequate and reliable documentation of the applied method shall be provided". Within this documentation "it is important to provide supporting information to strengthen the rationale for the read-across" (ECHA Guidance on information requirements and chemical safety assessment Chapter R.6: QSARs and grouping of chemicals; section R.6.2.2.1 Read-across). The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the target substance can be predicted from the data on the source substances.

Therefore, in the absence of such documentation and only referring to your future assessment of the listed studies, ECHA cannot verify that the properties of praseodymium, zirconium oxide/hydroxide, and silica/silicates can be predicted from the data on the source substances. However, ECHA already notes that among the studies listed for further analysis there was no studies on prenatal developmental toxicity identified for two of the main compounds, notably praseodymium and zirconium oxide/hydroxide.

As detailed above, the request in the original decision was not met, and you are still required to provide the pre-natal developmental toxicity study (Annex IX, 8.7.2.; test method: EU B.31./OECD 414) in rats or rabbits, oral route.

Appendix 2: Procedural history

In accordance with Article 42(1) of the REACH Regulation, the Agency examined the information submitted by you in consequence of decision CCH-D-2114289282-44-01/F. The Agency considered that this information did not meet one or more of the requests contained in that decision. Therefore, a new decision-making process was initiated under Article 41 of the REACH Regulation.

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft of this decision was notified to the Member States Competent Authorities according to Article 51(1) of the REACH Regulation.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA notified you of the draft decision and invited you to provide comments within 30 days of the notification.

ECHA took into account your comments and did not amend the request(s).

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. This decision does not prevent ECHA from initiating further compliance checks on the present registration at a later stage.

2. The Article 42(2) notification for the original decision is on hold until all information requested in the original decision has been received.